CLAIMS

1. An implantable synthetic tissue.

2. A synthetic tissue according to claim 1, which is biologically organized in the third dimensional direction.

3. A synthetic tissue according to claim 1, which has biological integration capability with surroundings.

4. A synthetic tissue according to claim 3, wherein the biological integration capability includes capability to adhere to surrounding cells and/or extracellular matrices.

5. A synthetic tissue according to claim 1, which comprises cells.

6. A synthetic tissue according to claim 1, which is substantially made of cells and a material derived from the cells.

7. A synthetic tissue according to claim 1, which is substantially made of cells and an extracellular matrix (ECM) derived from the cells.

8. A synthetic tissue according to claim 7, wherein the extracellular matrix contains at least one selected from the group consisting of collagen I, collagen III, vitronectin and fibronectin.

9. A synthetic tissue according to claim 7, wherein the extracellular matrix contains collagen I, collagen III, vitronectin and fibronectin.

10. A synthetic tissue according to claim 7, wherein the extracellular matrix contains vitronectin.

11. A synthetic tissue according to claim 7, wherein the extracellular matrix contains fibronectin.

12. A synthetic tissue according to claim 7, wherein the extracellular matrix contains collagen I and collagen III, the collagen constitutes 5% to 25% of the tissue, and the ratio of the collagen I to the collagen III is between 1:10 and 10:1.

13. A synthetic tissue according to claim 7, wherein the extracellular matrix and the cells are integrated together into a three-dimensional structure.

14. A synthetic tissue according to claim 7, wherein the extracellular matrix is diffusedly distributed in the tissue.

15. A synthetic tissue according to claim 1, wherein an extracellular matrix is diffusedly distributed, and the distribution densities of the extracellular matrix in two arbitrary sections of 1 cm^2 in the tissue have a ratio within a range of about 1:3 to about 3:1.

16. A synthetic tissue according to claim 1, which is heterologous, allogenic, isologous, or autogenous.

17. A synthetic tissue according to claim 1, which is free of scaffolds.

18. A synthetic tissue according to claim 1, which is used

to implant cells.

19. A synthetic tissue according to claim 1, which is large sized.

20. A synthetic tissue according to claim 1, which has a volume of at least about 20 mm^3.

21. A synthetic tissue according to claim 1, which is flexible.

22. A synthetic tissue according to claim 1, which is expandable and contractile.

23. A synthetic tissue according to claim 1, which can withstand heart pulsation.

24. A synthetic tissue according to claim 1, which is biologically organized in all three dimensional directions.

25. A synthetic tissue according to claim 24, wherein the biological integration is selected from the group consisting of internal binding of extracellular matrix, electrical integration, and intercellular signal transduction.

26. A synthetic tissue according to claim 1, which has a tissue strength which allows the synthetic tissue to be clinically applicable.

27. A synthetic tissue according to claim 26, wherein the strength is a break strength of about 0.02 N to about 2 N.

28. A synthetic tissue according to claim 26, wherein the

tissue strength is sufficient to provide self-supporting ability.

29. A synthetic tissue according to claim 28, wherein the self-supporting ability is characterized in that the synthetic tissue is not substantially broken when the synthetic tissue is picked up using forceps having a tip area of 0.05 to 3.0 mm^2.

30. A synthetic tissue according to claim 28, wherein the self-supporting ability is characterized in that the synthetic tissue is not broken when the synthetic tissue is picked up with a hand.

31. A synthetic tissue according to claim 26, wherein the site to which the synthetic tissue is intended to be applied, includes a heart.

32. A synthetic tissue according to claim 26, wherein the site to which the synthetic tissue is intended to be applied, includes an intervertebral disk, a meniscus, a cartilage, a bone, a ligament, or a tendon.

33. A synthetic tissue according to claim 26, wherein:

the synthetic tissue is a cartilage, an intervertebral disk, a meniscus, a ligament, or a tendon; and

the synthetic tissue remains attached without an additional fixation procedure, after the synthetic tissue is implanted into an injured portion of the intra-articular tissue.

34. A method for producing a synthetic tissue, comprising

the steps of:

A) providing cells;

B) placing the cells in a container, the container having cell culture medium containing an ECM-synthesis promoting agent and having a sufficient base area which can accommodate a synthetic tissue having a desired size;

C) culturing the cells in the container along with the cell culture medium containing the ECM synthesis promoting agent for a period of time suffificent for formation of the synthetic tissue having the desired size; and

D) detaching the cells from the container.

35. A method according to claim 34, wherein a stimulus for inducing tissue contraction is applied in the detaching step.

36. A method according to claim 35, wherein the stimulus includes a physical or chemical stimulus.

37. A method according to claim 36, wherein the physical stimulus includes shaking of the container, pipetting, or deformation of the container.

38. A method according to claim 34, wherein the detaching step includes adding an actin regulatory agent.

39. A method according to claim 38, wherein the actin regulatory agent includes a chemical substance selected from the group consisting of actin depolymerizing agents and actin polymerizing agents.

40. A method according to claim 39, wherein the actin depolymerizing agent is selected from the group consisting of Slingshot, cofilin, cyclase associated protein (CAP),

actin interacting protein 1 (AIP1), actin depolymerizing factor (ADF), destrin, depactin, actophorin, cytochalasin, and NGF (nerve growth factor).

41. A method according to claim 39, wherein the actin polymerizing agent is selected from the group consisting of RhoA, mDi, profilin, Rac1, IRSp53, WAVE2, ROCK, LIM kinase, cofilin, cdc42, N-WASP, Arp2/3, Drf3, Mena, lysophosphatidic acid (LPA), insulin, platelet derived growth factor (PDGF) a, PDGFb, chemokine, and transforming growth factor (TGF) β.

42. A method according to claim 34, wherein the container is free of scaffolds.

43. A method according to claim 34, wherein the cells are first cultured in monolayer culture.

44. A method according to claim 34, wherein the ECM synthesis promoting agent includes TGFβ1, TFGβ3, ascorbic acid, ascorbic acid 2-phosphate, or a derivative or salt thereof.

45. A method according to claim 44, wherein the ascorbic acid, ascorbic acid 2-phosphate, or the derivative or salt thereof is present at a concentration of at least 0.1 mM.

46. A method according to claim 44, wherein the TGFβ1 or TFGβ3 is present at a concentration of at least 1 ng/ml.

47. A method according to claim 34, wherein the cells are placed at a concentration of 5×10^4 to 5×10^6 cells per 1 cm^2, and the ECM synthesis promoting agent is ascorbic acid, ascorbic acid 2-phosphate, or a derivative or salt thereof,

and the ascorbic acid, ascorbic acid 2-phosphate, or the derivative or salt thereof is provided at a concentration of at least 0.1 mM.

48. A method according to claim 34, further comprising causing the synthetic tissue to detach from the container and self-contract.

49. A method according to claim 48, wherein the detaching and self-contraction are achieved by providing a physical stimulus to the container.

50. A method according to claim 48, wherein the detachment and self-contraction are achieved by providing a chemical stimulus to the container.

51. A method according to claim 34, wherein the sufficient period of time is at least 3 days.

52. A method according to claim 34, wherein the sufficient period of time is at least 3 days and a period of time required for the synthetic tissue to be spontaneously detached from the container at a maximum.

53. A method according to claim 52, wherein the period of time required for the synthetic tissue to be spontaneously detached from the container is at least 40 days.

54. A method according to claim 34, further comprising:
causing the synthetic tissue to differentiate.

55. A method according to claim 54, wherein the differentiation includes osteogenesis, chondrogenesis,

adipogenesis, tendon differentiation, and ligament differentiaion.

56. A method according to claim 55, wherein the osteogenesis is performed in medium containing dexamethasone, β-glycerophosphate, and ascorbic acid 2-phosphate.

57. A method according to claim 56, wherein the medium contains at least one selected from the group consisting of BMP (bone morphogenetic protein)-2, BMP-4, and BMP-7.

58. A method according to claim 55, wherein the chondrogenesis is performed in medium containing pyrubic acid, dexamethasone, ascorbic acid 2-phosphate, insulin, transferrin, and selenious acid.

59. A method according to claim 58, wherein the medium contains at least one selected from the group consisting of BMP-2, BMP-4, BMP-7, TGF(transforming frowth factor)-β1 and TGF-β3.

60. A method according to claim 54, wherein the differentiation step is performed before or after the detaching step.

61. A method according to claim 54, wherein the differentiation step is performed after the detaching step.

62. A method according to claim 34, wherein the cell includes cells of 3 or more passages.

63. A method according to claim 34, wherein the cells include cells of 3 to 8 passages.

64. A method according to claim 34, wherein the cells are provided at a cell density of 5.0×10^4 to 5.0×10^6 cells/cm^2.

65. A method according to claim 34, wherein the cells include myoblasts.

66. A method according to claim 34, wherein the cells include fat-derived cells.

67. A method according to claim 34, wherein the cells include synovium-derived cells.

68. A method according to claim 34, wherein the cells include mesenchymal stem cells.

69. A method according to claim 68, wherein the mesenchymal stem cells are derived from an adipose tissue, a synovial membrane, a tendon, a bone, or a bone marrow.

70. A method according to claim 34, further comprising:

producing a plurality of the synthetic tissues and attaching the plurality of the synthetic tissues together to be integrated.

71. A cell culture composition for producing a synthetic tissue from cells, comprising:

A) an element for maintaining the cells; and

B) an extracellular matrix synthesis promoting agent.

72. A method according to claim 68, wherein the ECM synthesis promoting agent includes TGFβ1, TFGβ3, ascorbic acid,

ascorbic acid 2-phosphate, or a derivative or salt thereof.

73. A method according to claim 72, wherein TGFβ1 or TFGβ3 is present at a concentration of at least 1 ng/ml, or ascorbic acid, ascorbic acid 2-phosphate, or the derivative or salt thereof is present at a concentration of at least 0.1 mM.

74. A complex for reinforcing a portion of an organism, comprising cells and a component derived from the cells.

75. A complex according to claim 74, which has biological integration capability with surroundings.

76. A complex according to claim 75, wherein the biological integration capability include capability to adhere to surrounding cells and/or extracellular matrices.

77. A complex according to claim 74, which is substantially made of cells and a material derived from the cells.

78. A complex according to claim 74, which is substantially made of cells and an extracellular matrix derived from the cells.

79. A synthetic tissue according to claim 78, wherein the extracellular matrix is selected from the group consisting of collagen I, collagen III, vitronectin and fibronectin.

80. A complex according to claim 78, wherein the extracellular matrix and the cells are integrated together into a three-dimensional structure.

81. A complex according to claim 78, wherein the

extracellular matrix is provided on a surface of the complex.

82. A complex according to claim 78, wherein the extracellular matrix is diffusedly distributed on a surface of the complex.

83. A complex according to claim 74, wherein an extracellular matrix is diffusedly distributed on a surface of the complex, and the distribution densities of the extracellular matrix in two arbitrary sections of 1 cm^2 in the complex have a ratio within a range of about 1:3 to about 3:1.

84. A complex according to claim 78, wherein the extracellular matrix includes fibronectin or vitronectin.

85. A complex according to claim 74, which is heterologous, allogenic, isologous, or autogenous.

86. A complex according to claim 74, wherein the portion includes a bag-shaped organ.

87. A complex according to claim 86, wherein the bag-shaped organ includes a heart.

88. A complex according to claim 74, wherein the portion includes a bone or cartilage tissue.

89. A complex according to claim 74, wherein the portion includes avascular tissue.

90. A complex according to claim 74, wherein the portion includes an intervertebral disk, a meniscus, a ligament, or a tendon.

91. A complex according to claim 74, wherein the reinforcement is achieved by replacing the portion with the complex or providing the complex to cover the portion, or both.

92. A complex according to claim 74, which resists the expansion and contraction of the portion.

93. A complex according to claim 74, which has biological integration.

94. A complex according to claim 74, wherein the biological integration selected from the group consisting of internal binding of extracellular matrix, electrical integration, and intercellular signal transduction.

95. A complex according to claim 74, which is formed by culturing cells in the presence of an ECM synthesis promoting agent.

96. A complex according to claim 74, which has self-supporting ability.

97. A method for reinforcing a portion of an organism, comprising the steps of:

A) replacing the portion with a complex comprising cells and a component derived from the cells or providing the complex to cover the portion, or both; and

B) holding the complex for a sufficient period of time for biologically adhering the complex to the portion.

98. A method according to claim 97, wherein the adhesion

is achieved by adhesion between extracellular matrix and extracellular matrix.

99. A method according to claim 97, which has biological integration capability with surroundings.

100. A method according to claim 99, wherein the biological integration capability include capability to adhere to surrounding cells and/or extracellular matrices.

101. A method according to claim 97, which is substantially made of cells and a material derived from the cells.

102. A method according to claim 97, which is substantially made of cells and an extracellular matrix derived from the cells.

103. A method according to claim 102, wherein the extracellular matrix contains one selected from the group consisting of collagen I, collagen III, vitronectin and fibronectin.

104. A method according to claim 102, wherein the extracellular matrix contains all of collagen I, collagen III, vitronectin and fibronectin.

105. A method according to claim 102, wherein the extracellular matrix contains vitronectin.

106. A method according to claim 102, wherein the extracellular matrix contains fibronectin.

107. A method according to claim 97, wherein an extracellular

matrix is provided on a surface of the complex.

108. A method according to claim 97, wherein an extracellular matrix is diffusedly distributed on a surface of the complex.

109. A method according to claim 97, wherein an extracellular matrix is diffusedly distributed on a surface of the complex, and the distribution densities of the extracellular matrix in two arbitrary sections of 1 cm^2 have a ratio within a range of about 1:3 to about 3:1.

110. A complex according to claim 97, wherein an extracellular matrix is diffusedly distributed on a surface of the complex, and the distribution densities of the extracellular matrix in two arbitrary sections of 1 cm^2 have a ratio within a range of about 1:2 to about 2:1.

111. A method according to claim 97, which is heterologous, allogenic, isologous, or autogenous.

112. A method according to claim 97, wherein the portion includes a bag-shaped organ.

113. A method according to claim 112, wherein the bag-shaped organ includes a heart.

114. A method according to claim 97, wherein the complex resists the expansion and contraction of the portion.

115. A method according to claim 97, wherein the complex has biological integration.

116. A method according to claim 115, wherein the biological

integration selected from the group consisting of internal binding of extracellular matrix, electrical integration, and intercellular signal transduction.

117. A method according to claim 97, further comprising:

forming the complex by culturing the cells in the presence of an ECM synthesis promoting agent.

118. A method according to claim 97, wherein the portion is a heart and the heart has a disease or disorder selected from the group consisting of heart failure, ischemic heart disease, myocardial infarct, cardiomyopathy, myocarditis, hypertrophic cardiomyopathy, dilated phase hypertrophic cardiomyopathy, and dilated cardiomyopathy.

119. A method according to claim 97, wherein the portion includes an avascular lesion.

120. A method according to claim 97, wherein the portion includes a vascular lesion.

121. A method according to claim 97, wherein the portion includes a bone or a cartilage.

122. A method according to claim 97, wherein the portion includes an intervertebral disk, a meniscus, a ligament, or a tendon.

123. A method according to claim 97, wherein the portion includes a bone or a cartilage, and the bone or the cartilage is damaged or degenerated.

124. A method according to claim 97, wherein the portion

includes intractable fracture, osteonecrosis, cartilage injury, meniscus injury, ligament injury, tendon injury, cartilage degeneration, meniscus degeneration, intervertebral disk denaturation, ligament degeneration, or tendon degeneration.

125. A method according to claim 97, wherein the sufficient period of time is at least 10 days.

126. A method according to claim 97, wherein the complex has self-supporting ability.

127. A method according to claim 97, which has biological integration capability with surroundings.

128. A method according to claim 97, which is substantially made of cells and an extracellular matrix derived from the cells.

129. A method according to claim 97, further comprising implanting another synthetic tissue.

130. A method according to claim 129, wherein the other synthetic tissue is an artificial bone or a microfibrous collagen medical device.

131. A method according to claim 97, which is substantially made of cells and an extracellular matrix derived from the cells, wherein the other synthetic tissue is an artificial bone or a microfibrous collagen medical device.

132. A method according to claim 130, the artificial bone includes hydroxyapatite.

133. A method for treating a portion of an organism, comprising the steps of:

A) replacing the portion with a complex comprising cells and a component derived from the cells or providing the complex to cover the portion, or both; and

B) holding the complex for a sufficient period of time for restoring a condition of the portion.

134. A method according to claim 133, wherein the treatment is for the treatment, prevention, or reinforcement of a disease, disorder, or condition of a heart, a bone, a cartilage, a ligament, a tendon, a meniscus, or an intervertebral disk.

135. A method according to claim 133, wherein the complex has self-supporting ability.

136. A method according to claim 133, wherein the complex has biological integration capability with surroundings.

137. A method according to claim 133, wherein the complex is substantially made of cells and an extracellular matrix derived from the cells.

138. A method according to claim 133, further comprising implanting another synthetic tissue in addition to the replacement or coverage of the portion.

139. A method according to claim 138, wherein the other synthetic tissue includes an artificial bone or a microfibrous collagen medical device.

140. A method according to claim 133, which is substantially made of cells and an extracellular matrix derived from the cells, wherein the other synthetic tissue includes an artificial bone or a microfibrous collagen medical device.

141. A method according to claim 139, the artificial bone includes hydroxyapatite.

142. A method for producing a synthetic tissue, comprising the steps of:

A) providing cells;

B) placing the cells in a container, the container having cell culture medium containing an ECM synthesis promoting agent and having a sufficient base area which can accommodate a synthetic tissue having a desired size;

C) culturing the cells in the container along with the cell culture medium containing the ECM synthesis promoting agent for a period of time suffificent for formation of the synthetic tissue having the desired size; and

D) regulating a thickness of the synthetic tissue by a physical or chemical stimulus to a desired thickness.

143. A method according to claim 142, wherein the physical stimulus includes shear stress between the synthetic tissue and the container, deformation of the base of the container, shaking of the container, or pipetting.

144. A method according to claim 142, wherein the chemical stimulus is obtained by using a chemical substance selected from the group consisting of actin depolymerizing agents and actin polymerizing agents.

145. A method according to claim 144, wherein the actin

depolymerizing agent is selected from the group consisting of Slingshot, cofilin, CAP (cyclase associated protein), AIP1 (actin interacting protein 1), ADF (actin depolymerizing factor), destrin, depactin, actophorin, cytochalasin, and NGF (nerve growth factor).

146. A method according to claim 144, wherein the actin polymerizing agent is selected from the group consisting of RhoA, mDi, profilin, Rac1, IRSp53, WAVE2, ROCK, LIM kinase, cofilin, cdc42, N-WASP, Arp2/3, Drf3, Mena, LPA (lysophosphatidic acid), insulin, PDGF (platelet derived growth factor), PDGFb, chemokine, and TGF (transforming growth factor) β.

147. A method according to claim 144, wherein the desired thickness is regulated by adjusting a ratio of the actin depolymerizing agent to the actin polymerizing agent.

148. A method according to claim 142, further comprising:

producing a plurality of the synthetic tissues and attaching the plurality of the synthetic tissues together to be integrated.

149. A tissue complex, comprising an implantable synthetic tissue and another synthetic tissue.

150. A tissue complex according to claim 149, wherein the implantable synthetic tissue is substantially made of cells and a material derived from the cells.

151. A tissue complex according to claim 149, wherein the implantable synthetic tissue is substantially made of cells and an extracellular matrix derived from the cells.

152. A tissue complex according to claim 151, wherein the extracellular matrix is selected from the group consisting of collagen I, collagen III, vitronectin, and fibronectin.

153. A tissue complex according to claim 151, wherein the extracellular matrix contains all of collagen I, collagen III, vitronectin, and fibronectin.

154. A tissue complex according to claim 149, wherein the other synthetic tissue includes an artificial bone or a microfibrous collagen medical device.

155. A tissue complex according to claim 154, the artificial bone includes hydroxyapatite.

156. A tissue complex according to claim 149, the implantable synthetic tissue is biologically integrated with the other synthetic tissue.

157. A tissue complex according to claim 156, wherein the biological integration is achieved via an extracellular matrix.

158. A composition for use in producing a synthetic tissue having a desired thickness, comprising a chemical substance selected from the group consisting of actin depolymerizing agents and actin polymerizing agents.

159. A composition according to claim 158, wherein the actin depolymerizing agent is selected from the group consisting of Slingshot, cofilin, CAP (cyclase associated protein), AIP1 (actin interacting protein 1), ADF (actin depolymerizing

factor), destrin, depactin, actophorin, cytochalasin, and NGF (nerve growth factor).

160. A composition according to claim 158, wherein the actin polymerizing agent is selected from the group consisting of RhoA, mDi, profilin, Rac1, IRSp53, WAVE2, ROCK, LIM kinase, cofilin, cdc42, N-WASP, Arp2/3, Drf3, Mena, LPA (lysophosphatidic acid), insulin, PDGF (platelet derived growth factor) a, PDGFb, chemokine, and TGF (transforming growth factor) β.